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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

23389 7590 09/30/2008

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ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
09/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,49-55,60-65,68-71 and 87-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,49-55,60-65,68-71 and 87-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 6/10/08 have been fully considered but they are not persuasive. Claims 45-46, 49-55, 60-65, 68-71, 87-91 are pending and under consideration. Claims 1-44, 47-48, 56-59, 66-67, 72-86, 92-132 are canceled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims **45-46, 62, 63, 64, 71, 87, 88, 89** remain rejected under 35 U.S.C. 102(b) as being anticipated by **Itskovitz-Eldor et al,** (Molecular Medicine, 6(2): 88-95, 2000) for the reasons of record of the office action mailed 1/18/08.

Applicants argue the Examiner's characterization of the reference is inaccurate. In Itzkovitz-Eldor, the hES cells are co-cultured with embryonic (fibroblast) cells which are used to maintain the cells in an undifferentiated state. Once the embryonic fibroblast cells are removed, the undifferentiated hES cells proceed to differentiate to form embryoid bodies. See page 89, 2nd column. Therefore, it is not until the hES cells are transferred do they differentiate, and by then the embryonic cells are removed. Thus, Applicant submits that the hES cells are not co-cultured with embryonic cells (fibroblasts) to induce differentiation, as presently claimed. See instant claim 45, for example. In fact, in Itskovitz-Eldor, the fibroblasts are necessary to maintain the hES cells in an undifferentiated state. Hence, Applicant respectfully submits that Itskovitz-

Eldor does not teach the co- culture of the hES cells and an embryonic cell to induce differentiation of the hES cells into mesoderm cells, as presently claimed.

These arguments ate not persuasive because the examiner accurately cites the Itzkovitz-Eldor reference, which anticipates the claimed invention for the following reasons which specifically, accurately and clearly the Itzkovitz-Eldor reference anticipates the claimed invention .

A) The instant claim 45 broadly requires culturing the hES cell in the presence of an embryonic cell and/or extracellular medium of an embryonic cell under conditions that induce differentiation of the undifferentiated stem cell into the mesoderm cell. The instant claim when broadly interpreted it encompasses any type of embryonic stem cell including embryonic fibroblast for culturing the hES cells. Itzkovitz-Eldor under materials and methods (p 89) specifically and very clearly teaches hES cells (H9 clone) were grown on mouse embryo fibroblasts in culture medium. Itzkovitz-Eldor teaches the hES cells (H9 clone 10) were grown on mouse embryonic fibroblasts in culture medium consisted of knockout DMEM, knockout SR, glutamine, mercaptoethanol, non-essential amino acids, LIF and basic FGF and under those conditions, most of the cells were kept in an undifferentiated state (p 89, 2nd column last paragraph bridge to 2nd column 1st paragraph). Itzkovitz-Eldor teaches to induce formation of EBs, ES cells were transferred using either collagenase or trypsin to plastic Petri dishes to allow their aggregation and prevent adherence to the plastic and the ES cells were incubated in the petri dishes and the hEBs were grown in the same culture medium except that it lacked LIF and bFGF (p 89, 2nd column, 1st paragraph). Itzkovitz-Eldor teaches they examined the differentiation status of the cultured hEBs cultured under said conditions and from ES cells grown on mouse embryo fibroblasts as feeder cells (emphasis added) and found robust expression of the ζ-globin mesodermal marker demonstrating that the EBs had begun

differentiating and some significant differentiation also occured in the ES cells grown on feeders as demonstrated by by low levels of the ζ-globin mesodermal marker (emphasis added) (see p 91, under results 2nd column). Moreover, Itzkovitz-Eldor teaches the differentiating cells acquired characteristic morphologies, distinct for hEB regions expressing functional markers as evident from the appearance of pulsing muscle cells as depicted in figure 4 the cardiac muscle differentiation depicted in a pulsing EB expressing a-cardiac actin (see p 93 1st and 2nd column and figure 4).

Thus, Applicants incorrectly argue that that the hES cells are not co-cultured with embryonic cells (fibroblasts) to induce differentiation, in the cited Itzkovitz-Eldor reference.

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **45-46, 49-55, 60-65, 68-71, 87-91** remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Itskovitz-Eldor et al,** (Molecular Medicine, 6(2): 88-95, 2000) in view of **Sugi et al,** (Developmental Dynamics, 200: 155-162, 1994); **Zhu et al,** (Developmental Dynamics, 207: 429-438, 1996); **Lough et al,** (Developmental Dynamics, 217: 327-342, 2000); **Klug et al,** (J Clin Invest, 98: 216-224, 1996) for the reasons of record of the office action mailed on 1/18/08.

Applicants argue that Itskovitz-Eldor fails to provide the necessary teaching as a primary reference to form a basis for combining with other references. As submitted above, the co-culture of the hES cell and the mouse embryonic (fibroblast) cell does not induce differentiation, and does not represent a condition that induces differentiation, of the undifferentiated hES cell into a mesoderm cell. The co-culture of hES cells with the mouse embryonic cell (fibroblast) is to ensure that the hES cells maintain their undifferentiated state. It is not until the hES cells are removed from the co-culture that embryoid bodies cells are formed. See, e.g., on page 89, 2na column of the reference, it is stated that "To induce formation of EBs, ES cells were transferred using collagenase..." Therefore, Itzkovitz-Eldor does not teach the use of a co-culture system to induce the hES cells to differentiate into a mesodermal cell. Applicants argue that these fundamental deficiencies of Itzkovitz-Eldor are not cured by the secondary reference to Sugi, as Sugi does not teach differentiation of an undifferentiated human stem cell to a mesoderm cell. Rather, Sugi teaches differentiation of a mesoderm cell to a terminally differentiated cardiomyocyte. In fact, Sugi's teaching is directed to the effect of endodermal cells on the terminal differentiation of mesodermal cells into cardiac myocytes. Hence, Sugi is a citation that relates to a different stage of the differentiation process. The Examiner contends that Sugi provides sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of Sugi into the hES cell culture system of Itzkovitz-Eldor for inducing differentiation of an undifferentiated hES cell. Applicant respectfully disagrees with the Examiner's contention. Sugi's teaching is directed to the effect of endodermal cells on the terminal differentiation of mesodermal cells into cardiac myocytes. There is no teaching or suggestion in Sugi for whether endodermal cells would have any impact on undifferentiated cells, such as undifferentiated hES cells, which are the starting cells of the presently claimed methods.

A) With regard to Itzkovitz-Eldor Applicant's arguments are not persuasive for the same reasons as discussed above.

Thus, Itzkovitz-Eldor teaches the use of a co-culture system to induce the hES cells to differentiate into a mesodermal cell (see response to arguments under *35 USC § 102*(b) supra).

B) With regard to the Applicant's arguments that there is no teaching or suggestion in Sugi for whether endodermal cells would have any impact on undifferentiated cells, such as undifferentiated hES cells, which are the starting cells of the presently claimed methods are not persuasive because Sugi teaches that the anterior endoderm cells regulate the terminal differentiation as opposed to the growth of presumptive cardiac myocytes in mesoderm from the anterior lateral plate (abstract). Sugi suggests that cells of the anterior endoderm/mesoderm specifically regulate the terminal differentiation of cardiomyocytes (p 159, 2nd column, last paragraph bridge p 160, 1st column, 1st paragraph). As such, Sugi et al provide sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of the Sugi into the hES cells culture system of **Itskovitz-Eldor et al** for inducing differentiation of a undiffentiated hES cells by culturing the hES cell in the presence of endodermal culture conditions for the induction of differentiation of undifferentiated hES cells. Sugi suggests that cells of the anterior endoderm/mesoderm specifically regulate the terminal differentiation of cardiomyocytes (p 159, 2nd column, last paragraph bridge p 160, 1st column, 1st paragraph). Sugi shows that only anterior endoderm cells were able to cause terminal differentiation in stage 6 mesoderm (p 156, 1st column, 3rd paragraph). Sugi demonstrates that stimulation of cardiogenesis by anterior endoderm was observed when the germ layers were co-cultured as a contiguous co-explant and when the germ layers were separated and co-cultured at opposite sides of the culture dish (figures 1 and 2). Sugi also describes a distance as long as 2 mm

separated the germ layers at the commencement of the culture period. Sugi suggests the need to co-culture said explants separated by semi-permeable membrane (p 158, bridge 1st and 2nd column). Sugi teaches that the anterior endoderm cells regulate the terminal differentiation as opposed to the growth of presumptive cardiac myocytes in mesoderm from the anterior lateral plate (abstract). As such, Sugi et al provide sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of the Sugi into the hES cells culture system of **Itskovitz-Eldor et al** for inducing differentiation of a undiffentiated hES cells by culturing the hES cell in the presence of endodermal culture conditions for the induction of differentiation of undifferentiated hES cells

C) Applicants argue Applicant that Zhu and Lough both relate to the terminal differentiation of mesoderm cells to cardiomyocytes. Therefore, these citations are not relevant to the differentiation of hES cells or of any other unspecified undifferentiated cells.

These arguments are not persuasive because Zhu and Lough both make up the deficiency for the embryonic cell is derived from visceral endoderm tissue or derived from visceral endoderm-like tissue, or derived from an early post-gastrulation embryo or wherein the visceral endoderm-like tissue is an embryonic cell line or wherein the embryonic cell line is an END-2 cell line or wherein the embryonic cell line is derive from mouse embryo E7.5 and not for a terminal differentiation of mesodermal cells to cardiomyocytes because Itzkovitz-Eldor teaches the use of a co-culture system to induce the hES cells to differentiate into a mesodermal cell see response to arguments under 35 USC 102(b) supra and Sugi's teaching is directed to the effect of endodermal cells on the terminal differentiation of mesodermal cells into cardiac myocytes. Therefore, in view of the totality of the prior art at the time the invention was made the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In view of the claim 1 in '790 is directed to a method of inducing cardiomyocyte differentiation of a stem cell by culturing the stem cells in the presence of a aprostaglandin, analogue or functional equivalent thereof alone or in combination with essential minerals, small molecules and protein growth factors of the FGF, IGF and BMP families, the double patenting rejection is Withdrawn.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
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